Acrylamide Scientific Issues: An Update

James R. Coughlin, Ph.D.

Coughlin & Associates

Laguna Niguel, California

jrcoughlin@cox.net

www.jrcoughlin-associates.com

Yum! Brands Presentation for CIC Meeting

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Presentation Topics

- Scope of the issue
- "The role or importance of the chemical matrix in which acrylamide is formed"
  - Complex chemical formation mechanisms
  - Beneficial effects of the Maillard Browning Reaction
- Some important toxicological considerations
- Recent dietary epidemiology studies
- Additional studies are needed to determine whether acrylamide in food poses a real risk to human health

[My Sept. 26 written submission and copies of references were contained in the CD-ROM that I supplied]

Swedish Discovery of Acrylamide in Foods

Tareke et al., *J. Agric. Food Chem.* 50: 4998-5006 (2002)

- Published in August 2002, following April 2002 press conference
- Acrylamide in foodstuffs was measured by two methods:
  - GC-MS detection [LD of 5 µg/kg] of brominated derivative
  - LC-MS-MS detection of underivatized acrylamide [LD of 10 µg/kg]
- Temperature/time dependence of acrylamide formation was shown:
  - Higher levels in carbohydrate-rich foods [150 - 4,000 µg/kg]
  - Moderate levels in protein-rich foods [5 - 50 µg/kg]
  - Acrylamide not detected in unheated control or boiled foods
  - Higher surface area foods had higher levels

Percent of Nutrients Contributed by Acrylamide-Containing Foods

- 38% of calories
- 33% of carbohydrates
- 36% of fiber
- 28% of fat
- 20% of calcium
- 47% of iron
- 25-35% of other nutrients
- 15% of vitamin A
- 34% of vitamin E
- 22-44% of vitamin B, vitamin C and folic acid

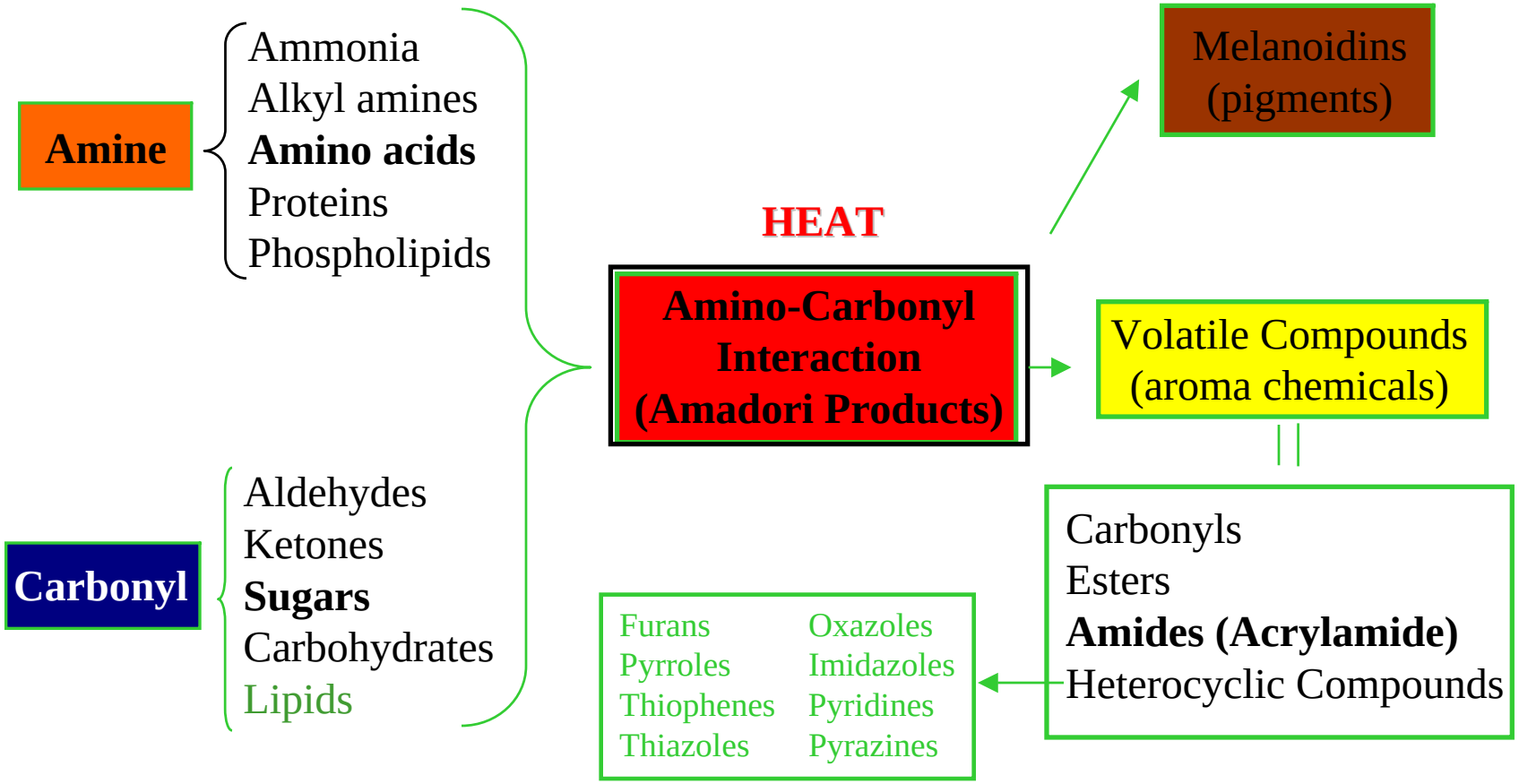
Source: Industry presentation to FDA's Food Advisory Committee, Feb. 24, 2003

Dietary Exposure Assessments in Europe and the U.S.

- Recent mean intake estimates are considerably lower than the original FAO/WHO high-end estimate of 56 µg/day

- Five studies [IARC/EPIC (Germany), Sweden, Netherlands, Norway and U.S.] show mean intake estimates of 8.4 – 38 µg/day

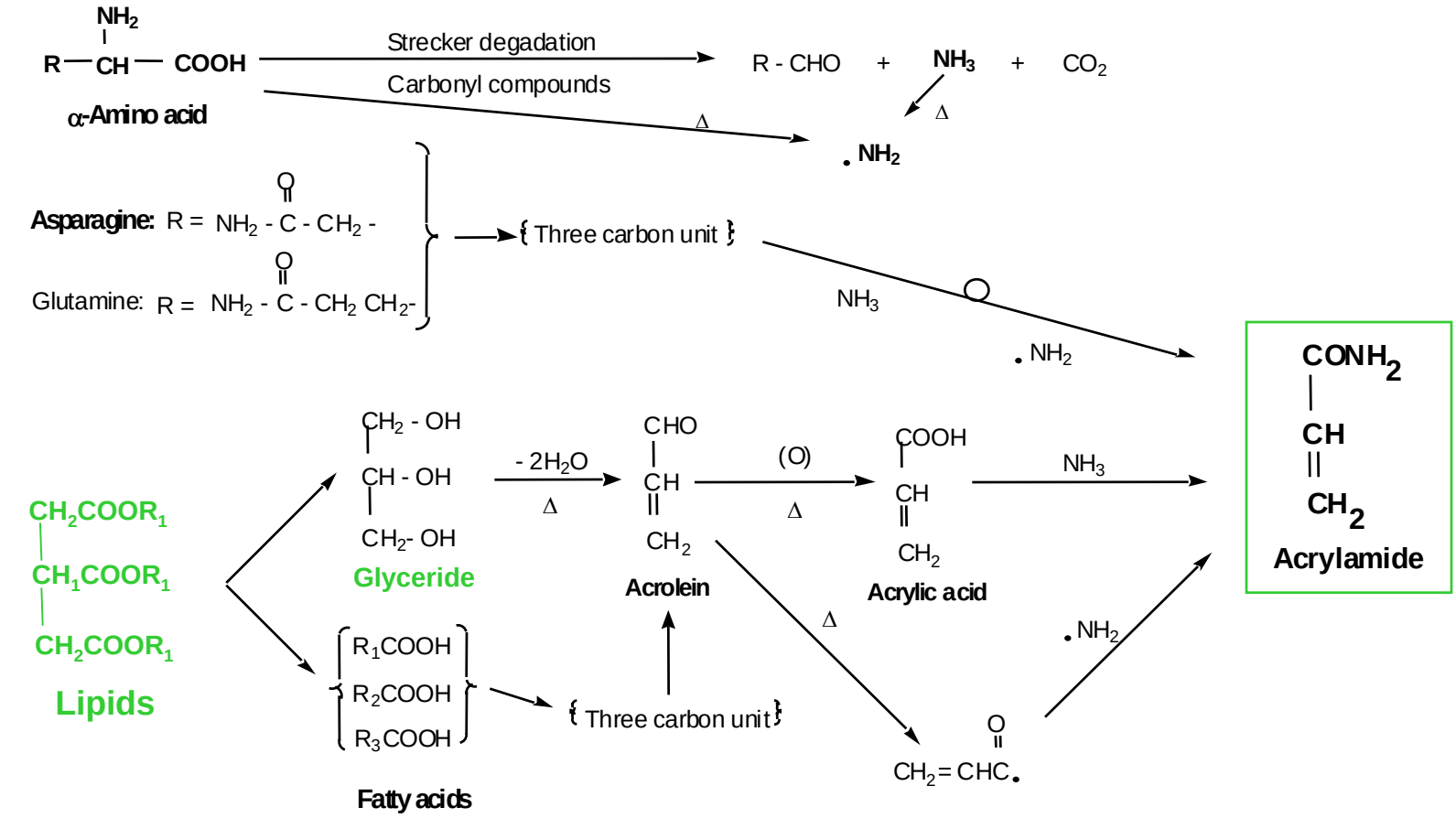
General Scheme of Maillard Browning Reaction



Chemical Formation Mechanisms of Acrylamide in Foods and Model Systems

- Several publications on formation mechanisms began appearing in September 2002
- Acrylamide was initially found in Maillard Browning Reaction model systems due to the reaction of glucose and asparagine, based on elegant labeling studies
- Professor Shibamoto was the first to show (earlier this year) additional complex mechanisms involving carbonyls (acrolein, acrylic acid) from heating ***lipids***, without the involvement of carbohydrates at all, and he showed the nitrogen source to be ***ammonia*** from the deamination of amino acids
- Nestle Research Center scientists in Switzerland (Stadler et al.) just demonstrated other reaction mechanisms not requiring asparagine

Proposed Formation Mechanisms of Acrylamide



Triolein: $R_1, R_2, R_3 = (CH_2)_7CH = CH(CH_2)_7CH_3$

Maillard Browning Reaction Issues Presented at the OEHHA Acrylamide Workshop (May 12, 2003)

- Benefits of the Maillard Browning Reaction (Coughlin and Shibamoto presentations):
  - Antioxidants produced during Maillard browning are known to be health protective for diseases linked to oxidative damage/stress (cancer, atherosclerosis, diabetes, inflammation, arthritis, immune deficiencies); many heterocyclic compounds have been shown to be antioxidants
  - Specific Maillard Reaction Products (MRPs) have anti-carcinogenic and anti-mutagenic effects, and they can also induce protective enzymes
  - While being one of the mechanisms for acrylamide formation, the Browning Reaction also plays a major role in determining the desirability and acceptability of food by consumers because of its impact on palatability

Important Toxicological Considerations

- Must study comparative metabolism and pharmacokinetics in rodents vs. humans to determine if acrylamide is metabolized differently by humans

- Humans have well-known acrylamide detoxifying enzymes that may protect them from low level exposures to carcinogens such as acrylamide:

  - Glutathione conjugation via glutathione transferase, then urinary excretion

  - DNA repair enzyme systems

Metabolic & Toxicokinetic Studies will Assist in Human Risk Assessment: Activation vs. Detoxification

- Metabolic activation:
  - Studies have shown that acrylamide is metabolized to glycidamide by the cytochrome P-450 2E1 oxidative enzyme pathway, the probable pathway for the carcinogenic effects of acrylamide
- Fortunately, major detoxification pathways also exist for acrylamide and glycidamide:
  - Glutathione pathway leads to enhanced excretion of acrylamide
  - Glycidamide is further metabolized by epoxide hydrolase to yield 2,3-dihydroxypropionamide
- **Key Point**: The balance of competing metabolic processes and their relative rates are important determinants of toxicity
  - These can differ between animals and humans and between high animal doses and drastically lower human intakes

MRPs Aid Detoxification by Enhancing the Expression of Protective Glutathione-S-transferase (GST) Enzymes

- Well-known Maillard reaction product, N^{ϵ}–carboxymethyllysine (CML), a 2-carbon adduct on protein, enhanced the expression of GST, the primary detoxification enzyme for acrylamide, in rats and in cultured human Caco-2 intestinal cells:
  - Rats fed casein-linked CML and bread crust-linked CML showed an inductive effect of CML on GST activity in the kidneys
  - Cell culture studies also confirmed these inductive effects
- Significance: while the browning reaction does create acrylamide, it also creates a protective chemical adduct – CML – resulting in increased detoxification of the acrylamide found in the same browned foods
- Studies are continuing on other MRPs for their ability to induce protective enzymes, which may have a significant impact on reducing the human risk from acrylamide, if any

Effects of dietary N^{ϵ}–carboxymethyllysine on expression of the biotransformation enzyme, glutathione-S-transferase, in the rat. Faist et al., Intl. Congress Ser. 1245:313-320 (2002)

First Cancer Epidemiology Study of Acrylamide in the Diet was Published

- Sweden's Karolinska Institute and Harvard School of Public Health; food frequency data and acrylamide levels; population-based case-control study of Swedish adults:
  - Large bowel cases (N = 591)
  - Bladder cases (N = 263)
  - Kidney cases (N = 133)
  - Healthy controls (N = 538)

- "We found consistently a lack of an excess risk, or any convincing trend, of cancer of the bowel, bladder, or kidney in high consumers of 14 different food items with a high (range 300-1200 μg kg^{-1}) or moderate (range 30-299 μg kg^{-1}) acrylamide content." (emphasis added)

- Found an inverse trend (p = 0.01) for large bowel cancer, with a 40% reduced risk in the highest compared to the lowest quartile

- "We found reassuring evidence that dietary exposure to acrylamide in amounts typically ingested by Swedish adults in certain foods has no measurable impact on risk of three major types of cancer." (emphasis added)

Ref. Mucci et al., Br. J. Cancer 88:84-89 (2003)

Second Cancer Epidemiology Study of Acrylamide in the Diet was Published

- Italy's Mario Negri Institute, IARC and Harvard School of Public Health; hospital-based case-control study in Italy and Switzerland between 1991-2000; food frequency questionnaire:
  - Large bowel cases (N = 1,953)
  - Breast cases (N = 2,569)
  - Ovary cases (N = 1,031)
  - Esophagus (395), oral cavity & pharynx (749), larynx (527)
  - Hospital controls for each cancer site

- "All the odds ratios (OR) for the highest vs. the lowest tertile of intake ranged between 0.8 - 1.1." (OR = 1.0 is defined as no association)

- Inverse trend ($p < 0.05$) found for large bowel and colon cancer overall

- "Thus, our data provide reassuring evidence for the lack of an association between moderate consumption of fried/baked potatoes and cancer risk at the investigated sites." (emphasis added)

Ref. Pelucchi et al., Int. J. Cancer 105:558-560 (2003)

Additional Studies Are Needed to Determine Whether Acrylamide in Food Poses a Real Risk to Human Health

- Does acrylamide in cooked food pose a real risk to humans?

  A reliable answer based on sound science demands a variety of complex studies to fill the significant data gaps in our current understanding of the risk, if any, posed to humans.

- A comprehensive risk assessment must include:
  - Rodent cancer bioassays with acrylamide in feed
  - Bioavailability in foods – acrylamide may be less bioavailable in some foods than in water
  - Biomarker and metabolic studies – to investigate exposures and toxic effects at potential target organs
  - Proper animal to human risk extrapolations
  - The existence and impact of detoxifying and protective enzymes that may reduce the impact of acrylamide on humans
  - Dietary epidemiology studies of large populations